Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

17β-Ethoxy-3-methoxy-8-isoestra-1,3,5(10)-triene

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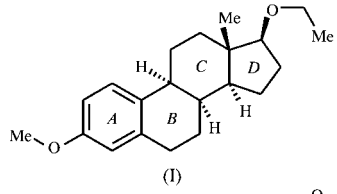
Received 3 June 2003
Accepted 19 June 2003
Online 22 July 2003

The conformation of the crystal of 17β-ethoxy-3-methoxy-8-isoestra-1,3,5(10)-triene, $C_{21}H_{30}O_2$, (I), has been established and compared with the molecular structure of a typical steroid estrogen 8-iso-analogue, (II). Calculations of distances separating some of the H-atom pairs in (I) and (II) by molecular-mechanical and semi-empirical methods revealed the similarity of the values to the H$\cdots$H distances obtained from X-ray analysis.

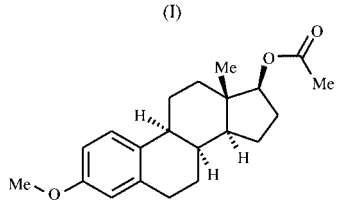
Comment

Steroid estrogens are widely used for hormone replacement therapy (Krempler *et al.*, 1995, and references therein; Vickers *et al.*, 1995, and references therein; Sotelo & Johnson, 1997), but many of these compounds increase the incidence of endometrium cancer (Sulak, 1997) and breast cancer (Colditz *et al.*, 1995; Vessay & Daly, 1997) under long-term application. One of the possible mechanisms contributing to carcinogenesis is the metabolic activation of estrogens by hydroxylation, leading to 16α-hydroxyestron formation (Palomino *et al.*, 1990; Kabat *et al.*, 1997; Shon *et al.*, 1997). Hence, any modifications of estrogen molecules that hinder such metabolic activation could reduce the incidence of carcinogenesis. At the same time, tolerance of target physiological activities to these modifications is required.

We have synthesized steroid estrogen 8-iso-analogues with a 17β-ethoxy group (Egorov *et al.*, 2003) and investigated their biological properties. This substituent could prevent ketone formation at the C17 position and could also shield the C16 position from metabolic hydroxylation. We found that such steroids, given orally to ovariectomized rats for 35 d, normalized serum cholesterol level and prevented mineral bone-content loss, which highlights the importance of investigating the molecular structure of such compounds. Structure investigations were carried out for 17β-ethoxy-3-methoxy-8-isoestra-1,3,5(10)-triene, (I), synthesized from 17β-acetoxy-3-methoxy-8-isoestra-1,3,5(10)-triene, (II), *via* the Brown reaction (Pettit & Piatak, 1962), and the crystal conformation (Fig. 1) was determined by X-ray analysis. Positional parameters, bond lengths, bond angles and torsion angles have been deposited in the Cambridge Structural Database (No. 164258; Allen, 2002) and presented by Shavva *et al.* (2001).



(I)



(II)

Ring *A* (C1–C5/C10) is planar and ring *B* (C5–C10) has a distorted 8α-half-chair conformation. Atoms C6 and C9 lie almost in the plane of ring *A*, whereas atoms C7 and C8 deviate by 0.33 (1) and -0.44 (1) Å, respectively, from the plane. The angle between the C5/C6/C9/C10 and C7/C8/C9 planes is 43.0 (1)°. Ring *C* (C8/C9/C11–C14) has a regular 9α,13β-chair conformation, and the angles between the C8/C11/C12/C14 plane ('chair bottom') and the C8/C9/C11 and C12/C13/C14 planes are 131.4 (2) and 131.9 (2)°, respectively. Ring *D* (C13–C17) has an almost regular 13β-envelope conformation, with an angle between the C14/C15/C16/C17 (base of the envelope) and C13/C14/C17 planes of 46.7 (1)°. The molecule is approximately 'flat' compared with the *B*-nor-8-iso-analogue (Egorov *et al.*, 2002); the plane of the aromatic ring makes an angle of 43.1 (2)° with the 'chair bottom' of ring *C* and an angle of 32.3 (2)° with the base of the envelope of ring *D*. The O1$\cdots$O2 distance, which is known to be important for binding to an estrogen receptor, is 10.916 (5) Å.

It is common knowledge that estrogen-receptor modulations of biological properties are determined mainly by the corresponding ligand–receptor complex structure (Anstead *et al.*, 1997; Gao *et al.*, 1999; Shiau *et al.*, 2002), and for this reason, attention is increasingly being focused on the analysis of such complexes with the aim of discovering biological-activity prediction principles for the design of new ligands

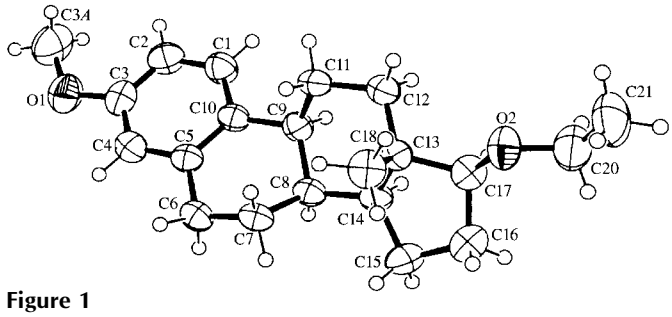


Figure 1
A view of the all-*S* enantiomer of (I), showing the atom-numbering scheme and displacement ellipsoids at the 50% probability level.

 DOI: 10.1107/S0108270103013775

(Shiau *et al.*, 1998, and references therein). At the first stage of investigation, ligand conformations based on X-ray analysis data and conformations calculated using molecular-mechanical methods are compared (Sedee *et al.*, 1985; Kayser *et al.*, 1995).

We decided to compare the molecular structure of (I) with the typical steroid estrogen 8-iso-analogue (II) (see *Scheme*), the X-ray data of which were reported by Starova *et al.* (2001). We found no difference in the general geometry of these molecules (Fig. 2). We also calculated interatomic distances (H1···H11α, H1···H11β, H1···H9α, H7α···H15α, H7α···H15β, H7β···H11β, H7β···H15α, H7β···H15β, H8α···H9α, H8α···H12α, H8α···H14α, H9α···H12α, H9α···H14α, H11α···H12α, H11α···H12β, H11β···H12α, H11β···H12β, H12α···H14, H12α···H17α, H14α···H17α, H15α···H16α, H15α···H16β, H15β···H16α, H15β···H16β and O1···O2) in (I) and (II) by molecular-mechanical (MM+) and semi-empirical (PM3) methods (Hypercube, 2000; Sizova & Baranovskiy, 2000), and compared the results with the values obtained from X-ray data. It is evident from Figs. 3 and 4 that the experimental and calculated H···H distances are very similar, and this fact is the basis for potential testing by the MM+ method in a preliminary study of the ligand–receptor complexes of 8-iso-analogues. We intend to report the results of such testing in the near future.

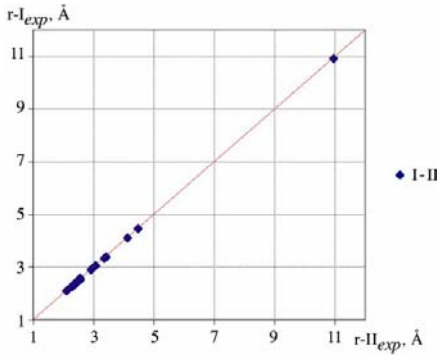


Figure 2
A comparison of X-ray interatomic distances in (I) and (II).

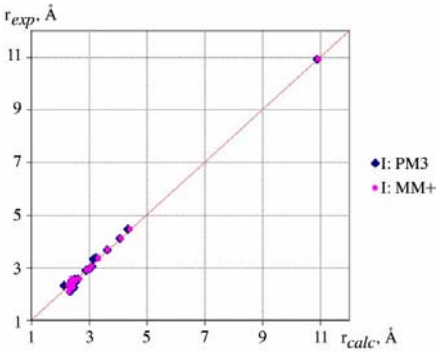


Figure 3
Interatomic distances in (I) calculated by molecular-mechanical (MM+) and semi-empirical (PM3) methods compared with X-ray analysis data.

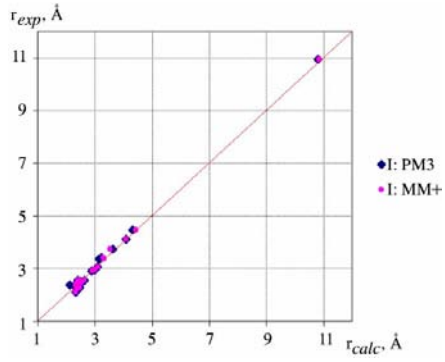


Figure 4
Interatomic distances in (II) calculated by molecular-mechanical (MM+) and semi-empirical (PM3) methods compared with X-ray analysis data.

Experimental

Colourless crystals of (I) suitable for diffraction analysis were obtained from a hexane/ethyl acetate solution by slow evaporation at room temperature.

Crystal data

$C_{21}H_{30}O_2$
M_r = 314.45
Monoclinic, $P2_1/n$
a = 14.316 (2) Å
b = 7.7313 (11) Å
c = 17.678 (3) Å
β = 112.43°
V = 1808.7 (4) Å^3
Z = 4
D_x = 1.155 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 162 reflections
θ = 3–28°
μ = 0.07 mm^{-1}
T = 293 (2) K
Plate, colourless
0.32 × 0.28 × 0.08 mm

Data collection

Bruker CCD area-detector diffractometer
φ and ω scans
10 591 measured reflections
4239 independent reflections
1359 reflections with $I > 2\sigma(I)$
R_{int} = 0.089
θ_{max} = 28.4°
$h = -15 \rightarrow 18$
$k = -10 \rightarrow 10$
$l = -23 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.096
S = 0.76
4239 reflections
209 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0288P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0122 (12)

H atoms were treated as riding, with C—H distances of 0.93–0.98 Å and U_{iso}(H) values equal to 1.5U_{eq} of the parent atom.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SAINT* (Bruker, 1997); data reduction: *SHELXTL* (Bruker, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); Software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1142). Services for accessing these data are described at the back of the journal.

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